DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 12, 15, 20, 23, 26, 28, 33 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Kamb, 20030027214.

Kamb disclose methods for detecting substrate-ligand interactions, more particularly polypeptide-ligand interactions or polypeptide-polypeptide interactions. The polypeptides may be individual polypeptides, or may alternatively be library polypeptides, including those of large or very large libraries and/or of native, endogenous polypeptides. Paragraph 0011.

Also disclosed are methods for identifying and quantifying such interactions. In some embodiments, the interacting substrate-ligand pairs may be detected with antibodies, for example fluorescent antibodies, and the interactions quantified via a FACS machine or CCD camera. Paragraph 0012.

In some embodiments, a unique polypeptide or other such substrate may be adhered to a location-determinable support, which correlates to the unique location from which a particular library polypeptide is derived, prior to exposure to the ligands.

In other embodiments the unique **polypeptide or substrate remains in a lysate** or other such solution, to which the randomizable ligand-bearing supports are added. The supports described herein may be microbeads, or may be a fixed solid support. The unique tag that identifies a particular ligand may be, for example, a fluorescent "bar code" or oligonucleotide tag. Paragraph 0024.

The general strategy of the methodology is exemplified as follows. A substrate pool of interest is selected--for example, a library of all or substantially all native polypeptides expressed by the human organism, or a selection of individual polypeptides of interest. A corresponding set of library polypeptides or individual polypeptides are generated in cells. Single colonies, each of which is expressing one particular polypeptide of interest, are selected and replated in order to generate single-cell clones (i.e., multiple copies of one particular cell, each cell expressing the same individual polypeptide or unique member of the polypeptide library). Each such clone is uniquely located at one particular location of an array--e.g., each particular well of a given 384 well plate contains a one particular clone. The expression products of each of those clones are then harvested from the cells, for example by generating soluble lysates that correspond to each of the plated clones. Thus, each well corresponds to the soluble lysate of one particular clone, which in turn corresponds to one individual polypeptide or one unique member of a polypeptide library. Alternatively, each member of a non-proteinaceous substrate pool of interest is individually arrayed at a unique location. Paragraph 0031.

As one exemplary use of the invention, a polypeptide library may be

screened against itself to generate a "protein interaction map"--i.e., an "n.times.n" matrix of interactions for all or substantially all native polypeptides of a human or other selected organism. By "native polypeptides" is meant polypeptides that are endogenous to a selected organism--i.e., that are encoded by the organism's genome and which may be expressed by that organism. Native polypeptides include functional subunits or "protein domains" of endogenous proteins. In such embodiments, the polypeptides of interest serve as both substrate and ligand--i.e., each randomizable support is adhered to multiple copies of one member of the polypeptide library, and each unique array location contains multiple copies of one member of the polypeptide library. Once each randomizable support bears its corresponding unique library polypeptide, the supports are pooled into one volume and mixed to form a fully integrated ligand collection--i.e., the pooled volume represents all ligand species. Next, ligand aliquots are drawn from this fully integrated ligand collection. Each aliquot contains a randomized, representative sampling of the ligands that is statistically likely to contain at least one copy of each species of ligand present in the pooled ligand volume. These ligand aliquots then are presented for interaction with each of the library polypeptides, either by simply adding an aliquot of integrated ligand-bearing supports to each uniquely located library polypeptide lysate within the library array or by first adhering the library polypeptides in the array to location-determinable supports and then exposing each such set of polypeptide-bearing supports (which bear only one type of polypeptide) to an integrated aliquot of randomizable supports. Paragraph 0034.

Interactions between substrates and ligands are then detected by fluorescent or other means, for example by use of a fluorescently tagged antibody. Interacting pairs are then culled out in a sorting or detection process, for example via FACS, so that the components of the various complexes may be identified. The identity of the substrate is determined by correlating it to the unique array location from which it was derived (either directly, or via the analogous location-determinable support). If the substrate is proteinaceous, then the DNA encoding the polypeptide produced by the original single-cell clone at that unique location of the library array may then be sequenced or otherwise characterized. The identity of the ligand is determined by evaluating the associated unique identification tag on the randomizable support to which that ligand is bound. If the ligands are also polypeptides that have been uniquely arrayed, the unique identification tag can be further correlated back to a single clone in its corresponding array location. Paragraph 0038

It is disclosed that the screening methods of the present invention can be adapted in a number of ways apparent to those of skill in the art to displacement screening. In one non-limiting embodiment, the substrate-ligand pairs are first formed, and are adhered to a solid support. Subsequently, these pairs are exposed to a secondary ligand. If the secondary ligand is capable of adhering to the substrate, then in many cases it will displace the first ligand. The substrate-secondary ligand pair can then be manipulate, enriched and analyzed according to the method of the invention. The secondary ligand may be a proteinaceous moiety such as, e.g., a polypeptide or glycoprotein from a variety of sources, or may be some other organic or inorganic

molecule. The secondary ligand also may be an endogenous molecule such as a hormone, antibody, receptor, peptide, enzyme, growth factor or cellular adhesion molecule, or may be a derivatized or wholly synthetic molecule. In particularly preferred embodiments of displacement screening, the secondary ligand is a small organic molecule. Paragraph 0039

It is also disclosed that in the case of screening the native cellular proteins of an organism, an expression library is created by standard techniques, generating a sufficient number of fragments of DNA so as to ensure that all protein domains are likely to be expressed in the library. Paragraph 0042. If a subcloning strategy is to be employed, the library polypeptide-encoding vectors may be introduced into E. coli and clones are selected. Paragraph 0043.

Once each desired polypeptide is being expressed by the corresponding host cells, the cells are lysed so as to release the polypeptides. This growth and lysis may be accomplished directly, in each unique array location that contains them (e.g., microtiter well). Alternatively, in some embodiments each single-cell clone may be grown in an intermediate location of larger size or volume, so that a greater number of cells may be generated and concentrated for lysis. In such embodiments, each concentrated volume of polypeptide is then either lysed and the lysate transferred to its corresponding, unique array location, or the concentrate is transferred to that array location and then lysed in situ. Each clonal lysate then is kept separate from every other, and in a unique location that can be referenced throughout the ligand screening process. Thus, each soluble lysate can be correlated back to its unique library array

location, and the identity of the library polypeptide ascertained thereby, as the soluble lysates are used in later ligand interaction screening steps. Paragraph 0054.

In order to screen a variety of ligands for interaction with a given polypeptide, the method generally requires using a support or substrate that will serve three functions; (a) it will adhere to the ligand of interest; (b) it will be fully randomizable, so that an aliquot containing a representative sampling of ligands may be presented to each polypeptide of interest, and (c) it will carry a unique identification tag that corresponds to the particular ligand adhered to its surface, and distinguishes it from other ligand-bearing supports. Paragraph 0061.

A variety of methods are suitable for providing each support with an identification tag that correlates to the ligand that the support will bear.
For example, the beads may be tagged with DNA tags in which the tags can be amplified and fingerprinted, or detected by hybridization. Alternatively or in conjunction, the beads may be tagged with fluorescent tags such as fluorescent barcodes, radio frequency tags, or mass tags detected by mass spectrometry. Paragraph 0064.

Once the beads are prepared with the desired fluorescent barcode or other such unique tag, the desired ligands (or secondary ligands) may be adhered to the beads, to form a series of uniquely tagged ligand sets. Paragraph 0070.

If the ligand to be adhered is proteinaceous, then a subset of uniquely tagged, derivatized beads is exposed to a corresponding expression product lysate which is collected in a particular location in, e.g., a 384 well array. The subset of

identically tagged beads is suspended in solution and added to each well by either a pipetting device or by means of a magnetic dispenser (in the event that the beads are magnetic). The beads are mixed with the lysate in the well for a sufficient time to permit binding. This step thus generates subsets of uniquely identified ligands on randomizable supports. Paragraph 0072.

For some applications, a CCD camera may be utilized to detect interacting substrate-ligand complexes. For example, in applications screening for interaction of a non-proteinaceous organic molecule with a polypeptide, a CCD system can be used to visualize interacting complexes, thereby providing both detection and quantification. The CCD camera can detect a variety of visual outputs, including without limitation fluorescent emissions, chemiluminescent emissions, and SPA (scintillation Proximity Assay) emissions. In the SPA format, one member of the interacting pair is radiolabeled using standard techniques, and the other member of the pair is adhered to a bead in which a radio-detecting scintillation component is incorporated in the interior of the bead. When the radiolabeled component interacts with the bead-bound component, a detectable scintillation signal is emitted. The beads can optionally be displayed on some surface, for example an identification grid with grid locations correlating to each unique array location, for scanning by the detector. Paragraph 0092.

One non-limiting example of CCD detection of fluorescent signals utilizes a scientific grade CCD camera incorporating a high quantum efficiency image sensor. The target molecules are distributed along the well bottoms of optically transparent

microtiter plates. The CCD, fitted with lenses and optical filters, acquires images of the through the optically transparent well bottoms. Fluorescent excitation of the fluorescent molecules is generated by appropriately filtered coherent or incoherent light sources. The resulting digital images are stored on a computer for subsequent analysis. Paragraph 0093.

Thus, as to claim 1, Kamb disclose generating lystes, the lysates comprising a plurality of proteins expressed by the cell population (paragraphs 0031 and 0034), and depositing the lysates at discrete sites creating an array (paragraph 0031, disclosing wells with lysates; and paragraph 0054.) It is understood that wells, without disclosure to the contrary, are non-porous, as is well known in the art. Binding reagents for the proteins are applied for binding to proteins in the lysate (paragraphs 0034; 0038-0039; 0072), and optical signals emanating from the arrays are measured and recorded (paragraph 0012; 0092-0093).

As to claims 3 and 5, see paragraph 0072, disclosing the step of adding to the lysate collected in the wells, uniquely tagged, derivatized beads for binding. (As to the limitation regarding different arrays for each protein to be detected, any subset of the array (wells) discussed in claim 1 above constitute a different array.)

As to claim 4, the different tags are distinguishable (paragraphs 0072 and 0093.)

As to claim 12, see for example paragraph 0054.

As to claims 15 and 26, see paragraph 0093.

As to claim 20, see for examples paragraphs 0042 and 0054 (it is understood that the proteins in the lysates encompass the recited proteins).

As to claim 23, see paragraph 0093.

As to claim 28, the probling light is delivered in a trans-illumination configuration [i.e., through the transparent well bottoms] (paragraph 0093).

As to claim 33, see paragraph 0093. It is noted that the plate with transparent well bottoms constitutes an optical waveguide divided into individual waveguiding areas.

As to claim 69, paragraph 0036 discloses use of the apparatus for screening against combinatorial library components.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 6-8, 14 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214.

The teachings of Kamb have been discussed above. However, Kamb does not appear to teach generating lysates for detection of expression products (paragraph 0031), and that a polypeptide library may be screened against itself paragraph (0034), there does not appear to be a discussion of providing lysates from more than one population of cells. However, providing lysates from a second population of cells in the

array (well plate) would have been within the skills of the ordinary artisan because the desirability of such simultaneously screening is well known in the art and is also discussed by Kamb in paragraph 005, which discloses the desirability of high-throughput screening for comparative information regarding protein interactions in different cell types or cell states [i.e., different population of cells]. Given the disclosure of the Kamb invention having the ability to screen a vast number of molecular interactions and correlate back to the lysate or library, and the discussion in paragraph 005, the skilled artisan would have understood that it is suggested that the Kamb invention be used for such comparative screenings. The Kamb invention, as discussed above, provides the ability to screen a vast number of molecular interactions with the ability to correlate to the particular lysate or polypeptide library (paragraphs 0011, 0031, 0034), and thus the skilled artisan would have had reasonable expectation of success in screening libraries from more than one population of cells.

As to claim 7 and 8, the skilled artisan would have understood that the different "cell states" as discussed above encompass sub-populations obtained from a common cell population, at different points in time, as may be desirable for study.
standard would have been within the skills of the ordinary artisan.

As to claim 14, providing the Kamb invention such that the amount of material deposited represents less than 1000 cells is within the skill of the ordinary artisan as this amount of lysates correlating to a respective number of cells falls within a workable range of the Kamb invention.

As to claim 29, measurement of fluorescence intensity is disclosed (paragraph 0152.)

Claims 9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214, in view of Shen et al., 6,458,829.

The teachings of Kamb have been discussed above. While Kamb discloses that the method can be used for any of various types of assays and can be adapted in a number of ways (paragraphs 0011, 0012 and 0039), Kamb does not disclose type of assay recited in claim 9, that is, wherein lysates are generated from different cell sub-populations that have been obtained from a common cell population and then treated or stimulated with different reagents and/or exposed to different cultivation conditions.

However, such assay techniques are well known in the art, and such is also exemplified by Shen et al. as an in vitro model for a disease for performing studies to detect potential therapeutic compounds (column 2, lines 18-45.)

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214, in view of Gundersen et al., 20030129749.

The teachings of Kamb have been discussed above regarding claim 1. It is further recited in claim 10 that the different lysates are generated from diseased and

healthy cell populations. However, such assay technique s well known in the art for comparison, or study or diagnostic purposes, and such is exemplified by the disclosure of Gundersent et al. (see paragraph 0339 for example.) Thus use of lysates from diseased and healthy cell populations would have been obvious to the skilled artisan for comparison.

Claim 13 Is rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214, in view of Oh et al., 5,863,742.

The teachings of Kamb have been discussed above regarding claim 1. However, Kamb does not give an example of using lysates which contain added known concentration of compounds standards similar to the analytes to be determined as additives. However such technique for providing a standard is a well known technique in the assay art, and this is also exemplified by Oh et al. (see abstract for example).

Claims 16-19 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eipel et al., 6,737,024, in view of Kamb, 20030027214.

Eipel et al. discusses that the large number of synthesized compounds in combinatorial chemistry means that the efficiency of modern automated test systems can be fully exploited with regard to chemical diversity. Since, however, in contrast to

classical active substance synthesis, the chemicals to be investigated are not available in any desired amount on synthesis by means of combinatorial chemistry, only a restricted number of test systems can be examined because of the amounts of chemicals required in the test systems. Column 1, lines 57-65

It is also discussed that it has been found that the surface tension which hinders further miniaturization of the present microtiter plate technique to ever smaller reaction cavities (=wells), because thereby forces such as adhesion of the reaction liquid to the surface of the microtiter plates or the capillary forces are of increasing importance, and thus make it impossible to fill the reaction cavities and thus carry out a measurement, in very small microtiter plate wells, can be utilized advantageously for the supports according to the invention. Column 2, lines 28-36.

Hydrophilic measurement zones on the support mean areas on the support on which or in which the measurement is carried out after application of the reaction liquid and thus of the reactants (see number 2 in FIGS. 1, 3 and 4). They thus correspond to the wells in microtiter plates and are referred to hereinafter as "measurement zones or measurement points". Column 2, lines 37-43.

The hydrophilic measurement zones on the support are advantageously surrounded by a hydrophobic zone (see number 1 in FIGS. 1 to 4). This hydrophobic zone can be composed of at least one hydrophobic coating which covers the support completely or only partly with discontinuities. These discontinuities (see number 5 in FIGS. 1 to 4) are advantageously hydrophilic. Column 2, lines 44-50.

FIG. 2 depicts by way of example a support according to the invention

having the size of a microtiter plate. Column 3, lines 7-8.

The measurement zones can have any desired shape, with circular measurement zones being preferred. Column 3, lines 9-10.

The hydrophobic coating or coatings may be applied coherently to the support or else be provided with discontinuities of any design. They may also be in the form of separate zones around the measurement zones, with hydrophobic rings separating the hydrophilic measurement zones from one another being preferred. Column 3, lines 11-16.

The hydrophobic coating or coatings are intended to prevent the measurement zones spreading into one another and thus to make accurate measurement of individual reaction mixtures possible. Column 3, lines 17-20.

The hydrophobic coating can be a silane (see column 4, lines 11-31).

It is possible in principle to apply any desired number of measurement points onto a support, but the number of measurement points per cm.sup.2 is preferably greater than or equal to 10, particularly preferably greater than or equal to 15 and very particularly preferably greater than or equal to 20. Moreover, the reaction volumes applied are from a few nl up to some .mu.l, with volumes of less than 5 .mu.l being preferred, and of less than or equal to 1 .mu.l being particularly preferred. Column 3, lines 21-29.

The measurement points can be applied in any desired grids to the support, and square or rectangular grids are preferred. Column 3, lines 30-31.

The inert solid support may consist of a level, planar plate of a block of the same type or of a sheet of any desired shape and size, which may have small depressions (see FIG. 4) at the measurement zone points, with flat supports (see FIG. 3) being preferred. Rectangular or square supports are preferred, and rectangular supports with the size of a standard microtiter plate (127.5 mm.times.85.5 mm) or integral multiples of microtiter plates, which can be larger or smaller, are particularly preferred. Column 3, lines 33-45.

The support may consist, for example, of materials such as glass, ceramic, quartz, metal, stone, wood, plastic, rubber, silicon, germanium or porcelain. The materials can be used in pure form, as mixtures, alloys or blends or in various layers or after coating with, for example, a plastic or a paint for producing the supports according to the invention. Transparent supports made of quartz, glass, plastic, germanium or silicon, which are suitable for all visual tests such as microscopic, camera-assisted and laser-assisted tests, are preferably produced. Column 3, lines 46-55.

It is possible with these techniques if necessary to place different reagents and/or individual cells on the predetermined sites (measurement points) on the support surface and bring about reaction thereof. It is advantageous that, with the small volumes preferred according to the invention, in the range from a few nanoliters to a few microliters, mixing of the reactants by diffusion takes place very quickly so that no special mechanical mixing device is necessary. It is also possible, before the addition of liquid droplets for carrying out the actual analysis, for certain ligands, eg. proteins or nucleic acids, to be present on the support in adsorbed or chemically bound form

before metering in the measurement samples and the reagents. Column 4, line 59 to column 5, line 4.

The supports are suitable in principle for all analytical methods now carried out in microtiter plates, such as colorimetric, fluorimetric or densitometric methods. It is possible in these cases to use and measure light scattering, turbidity, wavelength-dependent light absorption, fluorescence, luminescence, raman scattering, ATR (=Attenuated Total Reflection), radioactivity, isotope labeling, pH shifts or ion shifts, advantageously alone or in combination, to mention only a few of the possible measured quantities here. Column 5, lines 28-37.

Analytical methods which can be carried out on the supports are the binding of antibodies to antigens, the interaction between receptors and ligands, the specific cleavage of substrate molecules by enzymes, the polymerase chain reaction (PCR), agglutination tests or the interaction between different or identical cell types such as enzyme assays, titration assays such as virus titration assays, erythrocyte or platelet aggregation assays, agglutination assays with latex beads, ELISA (=Enzyme-linked immunosorbent assay) or RIA (=Radioimmunoassay). Column 5, lines 38-48.

Thus, as to claim 16, Eipel et al. disclose an array with an adhesion-promoting layer on a support. As to the limitation regarding the adhesion-promoting layer having a thickness of less than 200 nm, this is within a workable range and thus would have been within the skills of the ordinary artisan.

As to claim 19, the Eipel et al. invention also has regions between discrete measurement areas [i.e., the hydrophobic coatings around the measurement zones] that are passivated to minimize nonspecific binding of reagents.

While Eipel et al. disclose that analytical methods which can be carried out on the supports are, for example, the binding of antibodies to antigens, the interaction between receptors and ligands (column 5, lines 38-48), Eipel et al. however do not given an example of an assay wherein the materials are in lysates. However, this type of assay is well known and is exemplified by Kamb.

It is disclosed by Kamb that in some embodiments the polypeptide, for example, remains in a lysate or other such solution, to which the reacting reagents are added. Paragraph 0024. The lysate from a cell population is placed in an array location, such as in a microtiter well. Paragraph 0054.

It is understood by the skilled artisan that the Kamb invention can be adapted for various forms of assays, and such is also suggested by Kamb (column 5, line 38-48). Moreover, given that performing reactions in which the binding molecule remains in the lysate during the reaction is known, as exemplified by Kamb, it would have been obvious to the skilled artisan that such types of assays can be performed using the Kamb device. That is, it would have been obvious to the skilled artisan to provide lysate from a cell population in an array according to the Eipel et al. invention for performing reactions with the molecules in the lysate, and the skilled artisan would have had reasonable expectation of success in performing a reaction because such reaction technique isknown in the art, as shown by Kamb.

As to claim 17, Eipel et al. disclose that the measurement zones, and the hydrophobic zones which separate them from one another (see number 1 in FIGS. 1 to 4), can be applied, for example, by microlithography, photoetching, microprinting or a micropunch technique or can be sprayed on using a mask technique. Photochemical processes which can be used to make the surfaces of plates or rolls specifically hydrophobic at particular points and hydrophilic at other points are known from the techniques for producing printing plates. It is possible with this technique to produce, for example, a grid of several thousand regularly arranged hydrophilic measurement zones (see number 2 in FIGS. 1, 3 and 4), surrounded by hydrophobic margins (see number 1 in FIGS. 1 to 4), in a simple manner on a support, eg. on a glass or metal plate. This may entail firstly one or more hydrophobic coatings being applied to the support, and subsequently the measurement zones being applied to the required points or, conversely, initially the hydrophilic measurement zones and then the hydrophobic zones, or both simultaneously, being applied. It is also possible to apply a plurality of hydrophilic measurement zones to the same point. Column 2, line 53 to column 3, line 6.

As to claim 18, Eipel et al. disclose that Methods suitable for applying sample material and reagents are all those able to meter amounts of liquid from a few nl to a few .mu.l, such as techniques used in ink jet printers. Drop formation can in this case take place by piezoelectric drop formation (ultrasound), piezoelectric drop ejection or ejection by evaporation (ink jet technique). Column 4, lines 37-47. These techniques can be used to place individual droplets in an accurately metered and targeted manner

on the individual hydrophilic measurement points of the multianalysis surface of the support by, for example, moving the support under one or more nozzles, which are arranged in parallel, in accordance with the rhythm of the metered liquid and in accordance with the preset grid, It is also possible likewise to move the metering device, for example consisting of at least one nozzle, over the support in accordance with the rhythm of the metered liquid and in accordance with the preset grid. Column 4, line 48-58.

As to claim 24, the silane or hydrophobic coating is optically transparent, given that it is a thin layer of molecules.

As to claim 25, the support may be transparent plastic [which is inherently moldable]. Column 3, lines 46-55.

Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214, in view of Craig et al., 6,972,198.

The teachings of Kamb have been discussed above. However, Kamb does not disclose a specific assay example in which the proteins to be detected are distinguished in the step of binding to added specific binding reagents, according to their occurrence in phosphorylaed and/or nonphosphorylated form (claim 21), nor a specific assay example in which the proteins to be detected are not distinguished in the step of binding

to added specific binding reagents (claim 22). However, an assay incorporating both of these limitations is taught by Craig et al.

More specifically, Craig et al. teach an assay to detect a modified, or alternatively an unmodified, protein, for example, a phosphorylated protein or unphosphorylated protein (col. 16, lines 12-41). Craig et al. teach constructing a peptide partner that will bind the substrate protein whether it is modified or unmodified (i.e., in both conformation states), and a second peptide partner which can bind to the substrate only if it is modified by binding to a newly exposed surface on the modified protein based on specific sequence recognition. Craig et al. teach that these two peptides can be labelled with appropriate fluorophores (e.g., fluoroscein and rhodamine) which will exhibit Fluorescence Resonance Energy Transfer (FRET) when they are in close proximity. Craig et al. teach that when the substrate is unmodified, only the first peptide will bind. Upon modification such as by a kinase or a phosphatase, the substrate undergoes a conformatonal change leading to unmasking of a binding motif which will bind the second peptide and therefore the activity of the modifying enzyme can be measured by monitoring FRET between the two bound, labelled peptides (col. 16, lines 21-41).

The protein, phosphorylated or not phosphorylated, is the protein to be detected. The step of binding the peptide that binds if the protein is modified (phosphorylated) is equivalent to the limitation regarding the protein not being distinguished according to the occurrence in phosphorylated form in the step of binding added specific binding reagents. The step of binding the peptide that binds only if the protein is unmodified (not phosphorylated) is equivalent to the claimed limitation of the protein not being

distinguished according to the occurrence in nonphosphorylated form in the step of binding to an added specific binding reagent.

Given that Kamb teach fluorescence detection and suggests adapting the use of the device for various detection assays, it would have been within the skills of the ordinary artisan to utilize the Kamb invention to perform the assay taught by Craig et al. for detection, and for the same reasons, the skilled artisan would have reasonable expectation of success in performing this fluorescence based assay using the Kamb apparatus and teachings.

Claim 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214, in view of Matson et al., 7,070,740.

The teachings of Kamb have been discussed above. However, Kamb does not teach that the probing light is delivered in epi-illumination configuration (claim 27) or trans-illumination (claim 28).

It is noted however that Kamb suggests that the wells can be used for detection of fluorescent signals (see paragraph 0093). While the exemplary embodiment shows that the light is detected through the bottom of the wells in paragraph 0093, it is understood that the invention is not limited to such detection technique.

Matson et al. teach that well plates for assays can be used for allowing light transmission and detection through the bottom of the well (trans-illuminating reading), or detection of signal from excitation by a reflected light (epi-illumination reading) can be used. Column 4, lines 32-51. It would have been within the skills of the ordinary

artisan to make modifications for epi-illumination reading as this is well known in the art and exemplified by Matson et al.

Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214, in view of Lackritz et al., 6,956,651.

The teachings of Kamb have been discussed above.

Claim 30 recites detection of changes in the refractive index of the measurement areas.

Claim 31 recites that the changes in the refractive index of the measurement areas is based on detection of changes in the pattern of interferences of light emanating from the planar solid support in the regions of the measurement areas generated on the solid support with light emanating from planes of interfaces to materials of different refractive index, caused by changes of phase differences between the light emanating from the interfaces and the light emanating from the regions of the measurement areas due to binding or desorption or displacement of applied specific binding partners, and wherein the interference light emanating from the different regions is measured in a locally spectrally resolved manner.

Claim 32 recites that the solid support is provided with a thin metal layer with a thickness of between 20nm and 200 nm, which is directly or mediated by an adhesion-promoting layer in contact with the measurement areas, and the detection of changes

in the refractive index on the measurement areas is based on detection of changes in the conditions for generating a surface plasmon resonance in the metal layer.

Lackritz et al. discloses that these features and suggest their combinations in microarray or microwell plates.

More specifically, Lackritz et al. disclose Optical Integrated Circuits (OIC) in surface plasmon resonance (SPR) Analysis Systems combined with micorarray or microwell plates to provide enhanced sensitivity, stability, speed of analysis and reduced size are disclosed. Using the OIC with other optical analysis methods to provide enhance analysis systems is also disclosed. (Abstract.)

The invention generally relates to bioanalysis systems and methods, such as surface plasmon resonance systems, involving optical circuits. In particular, the present invention relates to using optical circuits to improve management of light in bioanalysis systems such as surface plasmon resonance and providing improved sample arrays. Column 1, lines 10-15.

It is disclosed that surface plasmon resonance (SPR) is a "label free" method of assay development and is promising due to the possibility that it is faster to develop for any specific application and more reliable than label requiring methods such as those based on fluorescence. SPR systems and methods are known. Generally speaking, SPR is observed as a change such as a dip or reduction in intensity of light reflected at a specific angle from the interface between an optically transparent material and a thin metal film, and depends on among other factors the optical path length, i.e., the integral product of refractive index and physical thickness, of the medium and the

quantity and distribution of such refractive material close to the metal surface. A change of refractive properties at the metal surface, such as by the adsorption or binding of material with different optical properties (typically index of refraction) than the medium in which the SPR metal surface is immersed, causes a corresponding shift in the angle at which maximum SPR occurs and which can be related quantitatively to the quantity of material that binds or adsorbs. To couple the light to the interface with the assay such that SPR arises, alternative arrangements are used; either a metallized diffraction grating (Wood's effect), or a metallized glass prism or a prism in optical contact with a metallized glass substrate (Kretschmann effect). Column 2, lines 1-25.

Because Kackritz et al. teach that the disclosed invention can be combined with microarray or microwell plates, and Kamb suggest that various different detection techniques may be used, it would have been obvious to the skilled artisan to modify the well plate of the Kamb device to incorporate the features taught by Lackritz et al. for surface plasmon resonance detection, and also have reasonable expectation of success for the same reasons. Moreover, Lackritz et al. teach that the disclosed invention has the benefits of enhancement in sensitivity and speed of the analysis, which further would motivate the skilled artisan to combine the teachings.

Claims 34-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb, 20030027214, in view of Duveneck et al., 6,395,558.

Claim 34 recites that the optical waveguide is an optical film waveguide with a first transparent layer (a) facing the surface carrying the discrete measurement areas on a second transparent layer (b) with a refractive index lower than that of the first layer.

Claim 35 recites that the in-coupling of probing light into the transparent layer is in optical contact with optical in-coupling element(s), including prism coupler(s).

Claim 36 recites that the probing light is in in-coupled into the transparent layer (a) using granting structure(s) which are featured in the optically transparent layer.

Claim 37 recites that the light guided in the optically transparent layer (a) is out-coupled using grating structure(s) which are featured in the optically transparent layer.

Claim 38 recites that the detection of proteins takes place via a grating structure formed in the layer of the optical film waveguide based on changes in the resonance conditions for the in-coupling of probing light into layer (a).

Claim 39 recites that the optical waveguide is designed with a first optically transparent layer on a second optically transparent layer with lower refractive index than layer (a), wherein probing light is further in-coupled into the optically transparent layer (a) with the aid of one or more grating structures, which are featured in the optically transparent layer (a) and delivered as a guided wave to measurement areas located thereon

These optical feactures are taught by Duveneck et al. as part of a support material and optical detection features

More specifically, Duveneck et al. teach a planar optical sensor platform consisting of a preferably transparent support material (a) to which there are applied at least one thin, transparent waveguiding layer (b) and a recognition layer (c), the refractive index of the support material (a) being lower than the refractive index of the waveguiding layer (b) and the sensor platform being provided with a coupling grating for coupling in the excitation radiation, and the integrated-optical light pointer principle being realised by the waveguiding layer and the coupling-in grating. Column 2, line 66 to column 3, line 8.

It is also taught by Duveneck et al. that preferably the sensor platform has, physically separate from the first coupling grating, a second coupling grating for coupling out the wave guided in the waveguiding layer. Column 2, lines 9-11.

Also disclosed is use of one or more coupling gratings for the coupling-in and/or coupling-out of guided waves. The affinity sensory analysis using the direct detection method (by way of the change in refractive index) in which the shift in the coupling angle resonance, which, caused by adsorption or binding of molecules onto the surface, results from the change in refractive index, is determined. Column 2, lines 38-54.

An exemplary embodiment is a planar optical sensor platform consisting of a preferably transparent support material (a) to which there are applied at least one thin, transparent waveguiding layer (b) and a recognition layer (c), the refractive index of the support material (a) being lower than the refractive index of the waveguiding layer (b)

and the sensor platform being provided with a coupling grating for coupling in the excitation radiation, and the integrated-optical light pointer principle being realised by the waveguiding layer and the coupling-in grating. Column 2, line 66 to column 3, line 8.

The support materials may be for example glasses or quartz. For the economical production of sensor platforms it may be advantageous, however, to provide those support materials with a coating of low refractive index in which the grating structure for the coupling grating is incorporated. Column 7, line 64 to column 8, line 6. Moreover, it is disclosed that the coupling gratings may also be arranged at the waveguide/superstrate interface. Column 8, lines 7-8

Duveneck et al. teach that the detection can be carried out using known methods. Photodiodes, photocells, photomultipliers, CCD cameras and detector arrays, for example CCD rows, are suitable. For recording signals in accordance with the light pointer principle there are especially suitable position-sensitive and more especially laterally resolved detection methods, for example using CCD rows or arrays. It is also possible to use in the detection beam path further optical elements, such as mirrors, prisms, lenses, Fresnel lenses and graded index lenses, microlenses and microlens arrays for the purpose of projection onto the detectors. In the case of additional luminescence detection there are suitable for the selection of the emission wavelength known elements such as filters, prisms, monochromators, dichroic mirrors and diffraction gratings. Column 12, line 56 to column 14, line 3.

Duveneck et al. however does not teach an assay as recited in claim 1. However, such an assay is taught by Kamb.

Kamb disclose methods for detecting substrate-ligand interactions, more particularly polypeptide-ligand interactions or polypeptide-polypeptide interactions. The polypeptides may be individual polypeptides, or may alternatively be library polypeptides, including those of large or very large libraries and/or of native, endogenous polypeptides. Paragraph 0011.

Also disclosed are methods for identifying and quantifying such interactions. In some embodiments, the interacting substrate-ligand pairs may be detected with antibodies, for example fluorescent antibodies, and the interactions quantified via a FACS machine or CCD camera. Paragraph 0012.

In some embodiments, a unique polypeptide or other such substrate may be adhered to a location-determinable support, which correlates to the unique location from which a particular library polypeptide is derived, prior to exposure to the ligands. In other embodiments the unique polypeptide or substrate remains in a lysate or other such solution, to which the randomizable ligand-bearing supports are added. The supports described herein may be microbeads, or may be a fixed solid support. The unique tag that identifies a particular ligand may be, for example, a fluorescent "bar code" or oligonucleotide tag. Paragraph 0024.

The general strategy of the methodology is exemplified as follows. A substrate pool of interest is selected--for example, a library of all or substantially all native polypeptides expressed by the human organism, or a selection of individual

polypeptides of interest. A corresponding set of library polypeptides or individual polypeptides are generated in cells. Single colonies, each of which is expressing one particular polypeptide of interest, are selected and replated in order to generate single-cell clones (i.e., multiple copies of one particular cell, each cell expressing the same individual polypeptide or unique member of the polypeptide library). Each such clone is uniquely located at one particular location of an array--e.g., each particular well of a given 384 well plate contains a one particular clone. The expression products of each of those clones are then harvested from the cells, for example by generating soluble lysates that correspond to each of the plated clones. Thus, each well corresponds to the soluble lysate of one particular clone, which in turn corresponds to one individual polypeptide or one unique member of a polypeptide library. Alternatively, each member of a non-proteinaceous substrate pool of interest is individually arrayed at a unique location. Paragraph 0031.

As one exemplary use of the invention, a polypeptide library may be screened against itself to generate a "protein interaction map"--i.e., an "n.times.n" matrix of interactions for all or substantially all native polypeptides of a human or other selected organism. By "native polypeptides" is meant polypeptides that are endogenous to a selected organism--i.e., that are encoded by the organism's genome and which may be expressed by that organism. Native polypeptides include functional subunits or "protein domains" of endogenous proteins. In such embodiments, the polypeptides of interest serve as both substrate and ligand--i.e., each randomizable support is adhered to multiple copies of one member of the

polypeptide library, and each unique array location contains multiple copies of one member of the polypeptide library. Once each randomizable support bears its corresponding unique library polypeptide, the supports are pooled into one volume and mixed to form a fully integrated ligand collection--i.e., the pooled volume represents all ligand species. Next, ligand aliquots are drawn from this fully integrated ligand collection. Each aliquot contains a randomized, representative sampling of the ligands that is statistically likely to contain at least one copy of each species of ligand present in the pooled ligand volume. These ligand aliquots then are presented for interaction with each of the library polypeptides, either by simply adding an aliquot of integrated ligand-bearing supports to each uniquely located library polypeptide lysate within the library array or by first adhering the library polypeptides in the array to location-determinable supports and then exposing each such set of polypeptide-bearing supports (which bear only one type of polypeptide) to an integrated aliquot of randomizable supports. Paragraph 0034.

Interactions between substrates and ligands are then detected by fluorescent or other means, for example by use of a fluorescently tagged antibody. Interacting pairs are then culled out in a sorting or detection process, for example via FACS, so that the components of the various complexes may be identified. The identity of the substrate is determined by correlating it to the unique array location from which it was derived (either directly, or via the analogous location-determinable support). If the substrate is proteinaceous, then the DNA encoding the polypeptide produced by the original single-cell clone at that unique location of the library array may then be sequenced or

otherwise characterized. The identity of the ligand is determined by evaluating the associated unique identification tag on the randomizable support to which that ligand is bound. If the ligands are also polypeptides that have been uniquely arrayed, the unique identification tag can be further correlated back to a single clone in its corresponding array location. Paragraph 0038

It is disclosed that the screening methods of the present invention can be adapted in a number of ways apparent to those of skill in the art to displacement screening. In one non-limiting embodiment, the substrate-ligand pairs are first formed, and are adhered to a solid support. Subsequently, these pairs are exposed to a secondary ligand. If the secondary ligand is capable of adhering to the substrate, then in many cases it will displace the first ligand. The substrate-secondary ligand pair can then be manipulate, enriched and analyzed according to the method of the invention. The secondary ligand may be a proteinaceous moiety such as, e.g., a polypeptide or glycoprotein from a variety of sources, or may be some other organic or inorganic molecule. The secondary ligand also may be an endogenous molecule such as a hormone, antibody, receptor, peptide, enzyme, growth factor or cellular adhesion molecule, or may be a derivatized or wholly synthetic molecule. In particularly preferred embodiments of displacement screening, the secondary ligand is a small organic molecule. Paragraph 0039

It is also disclosed that in the case of screening the native cellular proteins of an organism, an expression library is created by standard techniques, generating a sufficient number of fragments of DNA so as to ensure that all protein domains are

likely to be expressed in the library. Paragraph 0042. If a subcloning strategy is to be employed, the library polypeptide-encoding vectors may be introduced into E. coli and clones are selected. Paragraph 0043.

Once each desired polypeptide is being expressed by the corresponding host cells, the cells are lysed so as to release the polypeptides. This growth and lysis may be accomplished directly, in each unique array location that contains them (e.g., microtiter well). Alternatively, in some embodiments each single-cell clone may be grown in an intermediate location of larger size or volume, so that a greater number of cells may be generated and concentrated for lysis. In such embodiments, each concentrated volume of polypeptide is then either lysed and the lysate transferred to its corresponding, unique array location, or the concentrate is transferred to that array location and then lysed in situ. Each clonal lysate then is kept separate from every other, and in a unique location that can be referenced throughout the ligand screening process. Thus, each soluble lysate can be correlated back to its unique library array location, and the identity of the library polypeptide ascertained thereby, as the soluble lysates are used in later ligand interaction screening steps. Paragraph 0054.

In order to screen a variety of ligands for interaction with a given polypeptide, the method generally requires using a support or substrate that will serve three functions; (a) it will adhere to the ligand of interest; (b) it will be fully randomizable, so that an aliquot containing a representative sampling of ligands may be presented to each polypeptide of interest, and (c) it will carry a unique identification tag that corresponds

to the particular ligand adhered to its surface, and distinguishes it from other ligand-bearing supports. Paragraph 0061.

A variety of methods are suitable for providing each support with an identification tag that correlates to the ligand that the support will bear. For example, the beads may be tagged with DNA tags in which the tags can be amplified and fingerprinted, or detected by hybridization. Alternatively or in conjunction, the beads may be tagged with fluorescent tags such as fluorescent barcodes, radio frequency tags, or mass tags detected by mass spectrometry. Paragraph 0064.

Once the beads are prepared with the desired fluorescent barcode or other such unique tag, the desired ligands (or secondary ligands) may be adhered to the beads, to form a series of uniquely tagged ligand sets. Paragraph 0070.

If the ligand to be adhered is proteinaceous, then a subset of uniquely tagged, derivatized beads is exposed to a corresponding expression product lysate which is collected in a particular location in, e.g., a 384 well array. The subset of identically tagged beads is suspended in solution and added to each well by either a pipetting device or by means of a magnetic dispenser (in the event that the beads are magnetic). The beads are mixed with the lysate in the well for a sufficient time to permit binding. This step thus generates subsets of uniquely identified ligands on randomizable supports. Paragraph 0072.

For some applications, a CCD camera may be utilized to detect interacting substrate-ligand complexes. For example, in applications screening for interaction of a

non-proteinaceous organic molecule with a polypeptide, a CCD system can be used to visualize interacting complexes, thereby providing both detection and quantification. The CCD camera can detect a variety of visual outputs, including without limitation fluorescent emissions, chemiluminescent emissions, and SPA (scintillation Proximity Assay) emissions. In the SPA format, one member of the interacting pair is radiolabeled using standard techniques, and the other member of the pair is adhered to a bead in which a radio-detecting scintillation component is incorporated in the interior of the bead. When the radiolabeled component interacts with the bead-bound component, a detectable scintillation signal is emitted. The beads can optionally be displayed on some surface, for example an identification grid with grid locations correlating to each unique array location, for scanning by the detector. Paragraph 0092.

One non-limiting example of CCD detection of fluorescent signals utilizes a scientific grade CCD camera incorporating a high quantum efficiency image sensor. The target molecules are distributed along the well bottoms of optically transparent microtiter plates. The CCD, fitted with lenses and optical filters, acquires images of the through the optically transparent well bottoms. Fluorescent excitation of the fluorescent molecules is generated by appropriately filtered coherent or incoherent light sources. The resulting digital images are stored on a computer for subsequent analysis. Paragraph 0093.

Thus, regarding the limitations of claim 1, Kamb disclose generating lystes, the lysates comprising a plurality of proteins expressed by the cell population (paragraphs

0031 and 0034), and depositing the lysates at discrete sites creating an array (paragraph 0031, disclosing wells with lysates; and paragraph 0054.) It is understood that wells, without disclosure to the contrary, are non-porous, as is well known in the art. Binding reagents for the proteins are applied for binding to proteins in the lysate (paragraphs 0034; 0038-0039; 0072), and optical signals emanating from the arrays are measured and recorded (paragraph 0012; 0092-0093).

It would have been obvious to the skilled artisan that such an assay taught by Kamb can be performed using the Duveneck et al. invention since the Duveneck et al. invention is not limited to a certain types of reagents or solvents, and it is understood that the Duveneck et al. invention can be adapted for performing various assays. Moreover, Kamb suggest that various detection techniques may be utilized, and thus further suggest, and provided reasonable expectation of success, in combining the teachings of the references.

Claim 40 recites that luminescences are generated upon excitation of detection reagents as claimed, nor that the detection reagents comprise luminescent labels, which can be excited at wavelengths 300 nm and 1100 nm. Luminescence detection is taught by Duveneck et al. as discussed above, and the use of various known labels, including those with the excitation wavelengths recited in the claim, would have been within the skills of the ordinary artisan.

Claim 41 recites different distinguishable detection reagents feature different emission wavelengths and/or different emission lifetimes. Such use of detecting

multiple different analytes is well known in the art and is well within the skill of the ordinary artisan.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that Kamb is different from the present invention in that in Kamb, lysates are deposited on a solid support that is suitable for adhering a desired polypeptide from a polypeptide containing lysate, and thus each measurement area comprises one unique polypeptide, whereas in the present invention, the lysates comprises a plurality of proteins. Applicant cites paragraphs 0031 and 0032 to support this argument. Those paragraphs are recited below for discussion purposes:

> The general strategy of the methodology is exemplified as follows. A substrate pool of interest is selected--for example, a library of all or substantially all native polypeptides expressed by the human organism, or a selection of individual polypeptides of interest. A **corresponding set of library polypeptides or individual polypeptides are generated in cells**. Single colonies, each of which is expressing one particular polypeptide of interest, are selected and replated in order to generate single-cell clones (i.e., multiple copies of one particular cell, each cell expressing the same individual polypeptide or unique member of the polypeptide library). Each such clone is uniquely located at one particular location of an array--e.g., **each particular well of a given 384 well plate contains a one particular clone**. The **expression products of each of those clones are then harvested from the cells, for example by generating soluble lysates** that correspond to each of the plated clones. Thus, **each well corresponds to the soluble lysate of one particular clone, which in turn corresponds to one individual polypeptide or one unique member of a polypeptide library.** Alternatively, each member of a non-proteinaceous substrate pool of interest is individually arrayed at a unique location. Paragraph 0031. Emphasis added.

> In the case of proteinaceous substrates, **the expression product of each lysate is then either (i) kept segregated in a unique location** (e.g., one particular well of a 384 well array); or (ii) exposed to a solid support that

is unique to that lysate source, and whose location may be tracked in order to identify the corresponding lysate source to which it was exposed. Such a solid support is termed herein, a "location-determinable support." Paragraph 0032, in part. Emphasis added.

Examiner finds that the reference teaches: 1) an array, in lysate, with one polypeptide per unique location (e.g., well); or 2) one *type* of cells and thus one *type* of polypeptide per array location.

The latter of the two is supported by the disclosure in paragraphs 0053-0054, as follows.

> Generation of Lysate Plates
> Once each desired polypeptide is being expressed by the corresponding host cells, the cells are lysed so as to release the polypeptides. This growth and lysis may be accomplished directly, in each unique array location that contains them (e.g., microtiter well). **Alternatively, in some embodiments each single-cell clone may be grown in an intermediate location of larger size or volume, so that a greater number of cells may be generated and concentrated for lysis.** In such embodiments**, each concentrated volume of polypeptide is then either lysed and the lysate transferred to its corresponding, unique array location, or the concentrate is transferred to that array location and then lysed in situ.** Each clonal **lysate** then is kept separate from every other, and **in a unique location** that can be referenced throughout the ligand screening process. Thus, each soluble lysate can be correlated back to its unique library array location, and the identity of the library polypeptide ascertained thereby, as the soluble lysates are used in later ligand interaction screening steps. (Paragraphs 0053-0054, emphasis added.)

Thus according to paragraph 954, each array location may alternatively have lysate with a **concentration** of the same type of polypeptide. A concentration of the unique polypeptide, from multiple single-cell clone implies that there are more than one polypeptide in the lysate per array location (e.g., well).

Moreover, Applicant's claims do not exclude an array of single polypeptides at each array location. For example, lines 3-4 of claim 1 do not require explicitly or

implicitly that the array comprises only one polypeptide at each array location. To the contrary, lines 3-4 encompass the generation of lysate plates as described by Kamb in paragraph 0054.

Applicant also argues that the ordinary artisan would not have had any motivation to modify the teaching of Kamb in immobilizing a plurality of proteins expressed by a cell population because he would have expected to lose the possibility to identify protein/ligand pair by training unique array location.

This is not persuasive because there is no reason to believe that repeating the above discussed method with a second population of cells would not work to identify the lysate or polypeptide through its array location. To the contrary, Kamb specifically teaches using an array location to correlate to the lysate or polypeptide (paragraph 0054), and thus, the skilled artisan would have been motivated to provide the same correlation when providing a different cell population, as would be desirable to conveniently, run parallel assays, as taught by Kamb.

Applicant further argues that the hydrophobic coating of Eipel is not equivalent to an adhesion-promoting layer. Examiner notes however that Eipel is relied upon for its teaching of hydrophilic measuring zones, which is equivalent to an adhesion-promoting zone.

It is further maintained by Applicant that none of the other cited references overcome the above asserted deficiencies of Kamb. Applicant argues that the Craig reference is not an immobilized assay wherein a plurality of proteins are deposited directly on the solid support or on an adhesion-promoting layer without modification or

separation of the proteinaceous analytes. Examiner emphasizes however that this aspect of the claimed invention is addressed by reference to the Kamb patent as discussed above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANN Y. LAM whose telephone number is (571)272-0822. The examiner can normally be reached on Mon.-Thurs. 9-7:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ann Y. Lam/
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